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# Accepted Manuscript

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### Highlights

- Utility of diuretic response (DR) measured during first 6 hours was tested in 1551 acute heart failure patients.
- DR within the first 6 hours performed as well as DR within the first 48 hours in predicting prognosis.
- The model incorporating serial changes in DR showed additive value with regard to prognostic prediction.

# Very early diuretic response after admission for acute heart failure

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**Running head:** Early DR in AHF

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## Abstract

### Background

In hospitalized heart failure patients, a poor diuretic response (DR) during the first days of hospital admission is associated with worse outcomes. However, it remains unknown whether diuretic response in the first hours has similar prognostic value. Moreover, data on the sequential change in DR during hospital admission are lacking.

### Methods and Results

DR (urine output per 40 mg furosemide-equivalent diuretics dose) was measured from 0 to 6 hours (DR6), 6 to 48 hours (DR6-48), and 0 to 48 hours (DR48) of the patient's arrival to the emergency department (ED) in 1551 patients with AHF (mean age 78 years old; 56% were male; and 48% were de-novo patients with heart failure). Patients with a poor DR within the first 6 hours were older age, had worse renal function and were already on diuretic treatment before admission. DR6 was only weakly correlated with DR6-48 (Spearman's  $\rho=0.273$ ;  $p<0.001$ ). DR6, DR6-48 and DR48 were all significantly associated with 60-day mortality independent of other prognostic factors. DR6 and DR48 showed comparable prognostic ability. However, the model combining DR6 with DR6-48 significantly exceeded both DR6 (NRI: 0.249,  $p=0.032$ ) and DR48 (NRI: 0.287,  $p=0.025$ ) with regard to 60-day mortality prediction.

### Conclusion

Both DR measured within the first 6 hours of ED arrival and DR measured during the first 48 hours in

patients with AHF have similar prognostic value, although they were moderately correlated. Changes in DR over time provide additional prognostic information.

**Keywords:** Diuretic resistance; Risk stratification, Prognosis

## Introduction

Intravenous loop diuretics are the cornerstone of treatment of hospitalized heart failure patients<sup>1-3</sup>. A poorer response to diuretic treatment was consistently related to worse outcomes. Poor renal function, low systolic blood pressure, ischemic etiology of heart failure, and diabetes are associated with poor diuretic response (DR) during 24-96 hours after hospital admission<sup>4-6</sup>. Therefore, strategies to improve DR in hospitalized heart failure patients are currently being considered. However, some important information for these strategies are currently missing. Most importantly, it is yet unknown how long we should measure DR in order to use it for risk stratification. In previous studies, the period of DR evaluation widely ranged from 24 hours to up to four days according to the definitions used in each study. If DR in the first hours has the same prognostic value as diuretic response during 24-96 hours after hospital admission, patients with a poor diuretic response can be identified at an earlier stage, and therefore treated earlier and more efficiently. However, the clinical significance of DR measured for periods shorter than 24 hours has not been elucidated.

Another point which remains unknown is clinical importance of temporal changes in DR. All previous studies evaluated DR for only one time period and DR has always been assumed to be constant during

the measurement period. However, no study has investigated the changes in DR over time and its prognostic implications.

REALITY-AHF was a prospective multicenter registry focusing on the association between acute phase treatment and prognosis of patients who had a heart failure hospital admission. Enrollment was performed from August 2014 to December 2015. Among the 20 participating hospitals, 9 were university hospitals and 11 were nonuniversity teaching hospitals. The primary objective of this registry was to investigate the prognostic impact of timing of treatment. Therefore, the amount of diuretics used and urine output were repetitively evaluated during first 48 hours after patient arrival. This study design enable us to evaluate and compare DR evaluated in different time period in terms of prognostic predict ability. In the current secondary analysis of REALITY-AHF , we aimed to: 1) evaluate if DR within 6 hours predicted prognosis as efficiently as DR within 48 hours; 2) test if serial changes in DR over time provided additional prognostic information in patients with AHF.

## Methods

### *Study design and patients*

This was a retrospective post-hoc analysis of the REALITY-AHF, in which 1682 consecutive patients with hospitalized AHF were prospectively registered. Enrollment was performed from August 2014 to December 2015. Among the 20 participating hospitals, 9 were university hospitals and 11 were nonuniversity teaching hospitals. The study design and primary outcomes have been described elsewhere <sup>7</sup>. Briefly, we enrolled patients aged  $\geq 20$  years diagnosed with AHF in the emergency

department (ED) within 3 hours from the first evaluation by caregivers and hospitalized through ED. The exclusion criteria were: 1) treatment with an intravenous drug started prior to arrival at ED, 2) history of heart transplantation, 3) patient on chronic peritoneal dialysis or hemodialysis, 4) acute myocarditis, and 5) acute coronary syndrome requiring emergency revascularization. Patients with a brain natriuretic peptide (BNP) level < 100 pg/mL or N-terminal-proBNP level < 300 pg/mL at baseline and patients with missing BNP and N-terminal-proBNP data were also excluded. All patients were enrolled at the ED and baseline data including physical findings, echocardiography, and laboratory data were collected at the ED.

We used prognostic endpoints of 60-day all-cause mortality. All patients were followed up for 1 year after discharge and prognostic information was prospectively collected. For those without follow-up data in the clinics where the patient was registered, prognostic data was obtained from telephone interviews with the medical records department of other medical facilities that managed the patient or with the family.

REALITY-AHF complies with the Declaration of Helsinki and Japanese Ethical Guideline for Medical and Health Research Involving Human Subjects. All participants were notified regarding their participation in the study and it was explained that they were free to opt out of participation at any time. The study protocol was approved by the ethics committee of each participating hospital. Study information including the objectives, inclusion and exclusion criteria, and the names of participating hospitals were published in the publically available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000014105) before the first patient was enrolled.



### *Diuretic response*

DR was defined as urine output (in mL) obtained per 40 mg of intravenous furosemide (or equivalent).

Oral furosemide was converted to half the dose of intravenous furosemide. The doses of oral loop diuretics that were considered equivalent to 40 mg intravenous furosemide were 10 mg torasemide and 60 mg azosemide. In REALITY-AHF, data on urine output was prospectively collected in pre-defined time-windows of 0 to 1.5, 1.5 to 6, 6 to 24, and 24 to 48 hours. However, data on the amount of intravenous and oral diuretics used were available only for the time windows of 0 to 6 and 0 to 48 hours. Therefore, we defined DR based on the urine output for three time windows: from 0 to 6 hours (DR6), 6 to 48 hours (DR6-48), and 0 to 48 hours (DR48).

### *Statistical analysis*

Data are expressed as mean and standard deviation for normally distributed variables, and as median with interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as numbers and percentages. The relationship between baseline characteristics and tertile groups of each DR6, DR6-48, and DR48 was examined using the one-way analysis of variance, Kruskal-Wallis, or chi-squared tests, where appropriate. The Cochran-Armitage trend test was used to test for a trend. When necessary, variables were transformed for further analyses. Correlations between DRs were evaluated using Spearman's rho.

In multivariable linear regression analyses, we constructed four models: 1) DR6 as outcome including

baseline (hour 0) variables as predictors to see which variables measurable at baseline can predict DR6;

2) DR6-48 as the outcome including baseline (hour 0) variables as predictors to see which variables measurable at baseline can predict DR 6-48; 3) DR6-48 as the outcome including DR6, heart rate, and systolic and diastolic blood pressure at 6 hours instead of these parameters measured at baseline (hour 0) in order to see how much of DR6-48 can be predicted by DR6 and other data available at the time of 6 hours after ED arrival; 4) DR48 as the outcome including baseline (hour 0) variables as predictors to see how much we can predict DR48 at the time of starting treatment. Multivariable linear regression analysis was performed using backward elimination method after including all variables with P value below 0.10 in univariate analysis. For prognostic analysis, we selected the following variables as preexisting and known prognostic factors: age, history of heart failure, New York Heart Association functional class, systolic blood pressure, hemoglobin, serum sodium, blood urea nitrogen, and BNP at admission. These variables were used for adjustment in multivariable Cox regression model. To account for missing covariate data, multiple imputation was used. We created 20 datasets using a chained-equations procedure<sup>8, 9</sup>. Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result using the method described by Barnard and Rubin<sup>10</sup>.

To evaluate the additive prognostic value of scores, we constructed the following three models for 60-day all-cause mortality: DR6 model constructed using DR6 alone; DR6 + DR6-48 model constructed incorporating DR6 and DR6-48, and DR48 model which used DR48 alone. Receiver operating characteristics (ROC) curves and their areas under the curve (AUCs) were evaluated. Confidence

intervals for the AUCs were obtained with 2000-bootstrap resampling. AUCs were compared using the Wald test based on the empirical standard deviation performing 2000-times resampling<sup>11</sup>. We also calculated the continuous (as opposed to the categorical) net-reclassification improvement (NRI) with its corresponding 95% confidence interval (CI) to evaluate the incremental predictive ability<sup>12</sup>.

Statistical analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL <http://www.R-project.org>). A two-sided P value < 0.05 was considered statistically significant.

## Results

### *Patient baseline characteristics for DR*

The study flow chart is shown in Figure 1. The REALITY-AHF cohort comprised of 1682 patients with AHF after excluding 80 of 1762 registered patients. Furthermore, we excluded another 22 patients who were discharged within two days, 88 patients who were neither treated with intravenous nor with oral loop diuretics and 21 patients whose data on diuretics use were missing; thus, 1551 patients remained. The mean age was 78 years old, 56% were male, 48% were de-novo patients with heart failure. After excluding patients without data on either urine output or diuretic use, data on DR6, DR6-48, and DR48 were available in 1071, 976, and 1471 patients, respectively. We also excluded patients with extremely high (>99<sup>th</sup> percentile) or low (<1<sup>st</sup> percentile) values for each DR (n=22 for DR6, n=20 for DR6-48, and n=29 for DR48) due to the unreliability of such values, and 1049, 956, and 1452 patients, respectively, were included in the final analysis.

Baseline characteristics according to tertile groups in DR6, DR6-48, and DR48 are described in Table 1 and Supplemental Table 1. Overall, poor DR was associated with older age, low blood pressure and heart rate, history of heart failure, and being treated with heart failure medication including diuretics, beta blocker, and aldosterone blocker. Regarding biomarkers, high white blood cell count, low serum albumin, low hemoglobin, low ALT, high creatinine and BUN, high potassium, high glucose, high C-reactive protein, and high BNP levels were associated with poor DR.

The results of univariate linear regression (Supplemental Table 2) and multivariable linear regression for each DR showed that older age, and higher serum creatinine and diuretic prescription at baseline were associated with poor DR in all three time periods (Table 2). In the model using DR6 and data at 6 hours, DR6 was the most powerful predictor of DR6-48; however, the final model which consists of all of independent predictors including DR6 explained only 8.8% of DR6-48. Supplemental Figure 1 shows the correlation of DR6 vs. DR48 and DR6 vs. DR6-48. DR6 was significantly but weakly correlated with DR6-48 (Spearman's  $\rho=0.273$ ,  $p<0.001$ ), and moderately correlated with DR48 (Spearman's  $\rho=0.544$ ,  $p<0.001$ ).

#### *Prognostic values of DR6, DR48, and DR6 plus DR6-48*

The overall 60-day follow-up rate was 97.4%, and 120 patients died during each follow-up period. Mortality rate for 60 days stratified by tertiles of DR6, DR6-48, and DR48 are shown in Figure 2, and poorer DR was significantly associated with higher 60-day mortality in all DRs ( $p$  for trend  $<0.01$  for all DRs). In the univariate and multivariable Cox regression analysis, all DRs were associated with 60-day

mortality even after adjustment for other prognostic factors when they were individually evaluated (Table 3). When both DR6 and DR6-48 were entered into the same Cox model, both were associated with 60-day mortality in univariate analysis, but only DR6 was significantly associated with 60-day mortality after adjustment for other covariates (Supplemental Table 3). Among 1551 patients, 172 (11%) were treated with tolvaptan and 627 (40.4%) were treated with carperitide within 48 hours. We checked the interaction between these drugs and prognostic value of diuretic response in the Cox model, and no significant interaction was found (Supplemental Table 4).

We grouped patients with available DR6 and DR6-48 into 9 groups according to the tertiles of DR6 and DR6-48, and more than half of patients in each tertile of DR6 were categorized into different tertiles of DR6-48. Unadjusted mortality tended to increase with decreasing DR6-48 in all tertile groups of DR6 (Figure 3).

To evaluate the difference in prognostic predictive ability, we compared the AUCs of the DR6 model, DR6 + DR6-48 model, and DR48 model for 60-day mortality (Table 4). There was no statistically significant difference in AUC and NRI between DR6 vs. DR48 for 60-day mortality. However, when DR6-48 was added to DR6, we found a net 24.9% improvement compared with DR6 and 28.7% improvement compared with DR48 in predicting 60-day mortality. We also compared DR6 and DR6-48 and did not observe significant difference in prognostic predict ability ( $p=0.768$  for AUC comparison; NRI: -0.005,  $p=0.948$ ).

## Discussion

In this study, we addressed two questions regarding DR which have remained unanswered in patients with AHF. For the first question “does very early DR carry the same predictive value as DR during hospital admission?”, we compared DR6 and DR48. DR measured within the first 6 hours of patient arrival in ED was significantly associated with 60-day mortality and performed comparable to DR measured within 48 hours. For the second question: “Does DR change overtime and what is its prognostic implication?”, we compared DR6 and DR6-48. Both entities showed only a notably weak association and DR6 poorly predicted DR6-48. Taken together with our finding that DR6-48 provides additive prognostic information on top of DR6, this suggests that patients with a poor DR in the first 6 hours are not necessarily the same patients as those with a poor DR from 6-48 hours, although both groups have poorer outcomes.

#### *Prognostic information of diuretic response within 6 hours*

The similar prognostic information of DR6 and DR48 is clinically and scientifically relevant as it enables an earlier identification of patients at high risk in the acute setting.

DR was initially introduced as an objective method to evaluate diuretic resistance, which was defined as body weight changes in 4 days per 40 mg of furosemide-equivalent diuretics<sup>5, 13</sup>. Although subsequent studies have consistently shown that poor DR is strongly and independently associated with a poor prognosis, very few studies compared the prognostic values between DR measured in different time periods. In the ASCEND dataset, DR based on weight change in up to 48 hours of admission and DR with urine output within 24 hours were evaluated<sup>6</sup>. The two DRs were modestly

correlated with each other, and both were associated with a combined endpoint of death and heart failure rehospitalization independent of other covariates. These findings are in line with ours in the sense that DR evaluated in a shorter period does not imply a less capable prognostication. Moreover, the study found that only DR based on urine output, but not DR in 24 hours based on body weight, was an independent predictor of 180-day mortality.

It is yet unclear whether changes in body weight, net fluid output, or urine output, should be used for measurement of DR in terms of better risk stratification, and there are some drawbacks in using urine output to determine DR compared to body weight<sup>14</sup>. Nevertheless, our study results may highlight the potential utility of very early DR based on urine output. Moreover, it may be difficult to weigh some patients before their condition is stabilized. This study, for the first time, showed the utility of short-term DR measurement in the ED setting in terms of risk stratification. Although the prognostic capability of DR based on urine or body weight in 6 hours or even within a shorter time period is yet to be determined, our study results expand the clinical utility of DR to the ED phase in which very prompt risk stratification of the AHF patient is required. Finally, our findings may contribute to better clinical study designs through a more accurate and prompt identification of high-risk AHF patients. This is also important as recent studies have highlighted the importance of early treatment in AHF patients<sup>7, 15, 16</sup>.

#### *Variability in diuretic response*

Since we could capture all patients from the beginning of treatment (i.e., arrival at ED), unlike in previous studies, it was possible to ascertain acute DR and its variability with time in AHF. Our study

results suggest that considerable inter-patient DR fluctuation occurs over time as less than half of the patients remained in the same tertile of DR in the two time periods, and DR6 and DR6-48 were weakly associated ( $\rho=0.275$ ,  $P<0.001$ ). Also, we found that it was difficult to predict DR6-48 even if DR6 was taken into consideration. These findings imply that the fluctuation of DR over time is not rare, and this fluctuation is not easily predictable. In contrast, findings from PROTECT study showed that DR based on weight change in 24 hours and on day 4 were well correlated<sup>17</sup>. This might be attributable to the difference in the definition of DRs, in the sense that body weight might not be as volatile as urine volume for reflecting sequential changes in DR. It could also be hypothesized that the majority of diuresis occurred mostly within 24 hours. Indeed, our results showed that only DR6 was associated with mortality when they were put together in the same multivariate Cox model. At the same time, however, taking both metrics into account was shown to contribute to better prognostic prediction and this implies the value of measuring serial changes in DR within 48 hours. Given that DR has been, by definition, configured with the assumption that diuretics yield urine output constantly during the measurement period, our finding is both scientifically and clinically relevant as it shows that DR is not constant but variable and that the fluctuation of DR is prognostic. The main driver of the DR fluctuation has yet to be elucidated. It could be the change in responsiveness to diuretic therapy itself. However, it could also be the action subsequently taken by physician in response to early DR.

### *Study Limitations*

In this retrospective post-hoc analysis, several study limitations need to be acknowledged. Our study



cohort were almost all Japanese and generalizability of our results is not clear. Moreover, almost a half of all patients were those without history of heart failure taking no heart failure drug at the time of admission. Although we checked the impact of history of heart failure on association between DR and prognosis, and found no significant interaction (data not shown), this point should be taken into account for interpretation of our study results. The protocol of the diuretic therapy was at the discretion of the physicians. Some patients were treated with the drugs (e.g. tolvaptan and carperitide) that might have affected the association between diuretic response and prognosis. This point should also be taken into account as a potential bias for our study results even though our interaction analysis results were not statistically significant. We did not have data on DR6 for all patients with DR48 data, as not all of patients with DR48 data were treated with furosemide within 6 hours. This might have resulted in selection bias and the limited applicability of early DR. By design, this registry enrolled only patients hospitalized through ED and the generalizability of our study results to other AHF populations hospitalized through non-ED pathways is not clear. Moreover, the generalizability of our study results to AHF patients who are not hospitalized and are directly discharged from ED should carefully be interpreted. We arbitrarily compared DR measured in two time periods (i.e. 6 and 48 hours); however, it is still unclear when and how frequently DR should be measured in order to optimize its prognostic value. Testani et al. showed that an equation using serum and urine creatinine concentration measured with a spot urine sample obtained one hour after diuretic use can accurately predict urine output<sup>18</sup>. Thus, the applicability of this study result to even early DR prediction is well justified. However, only bumetanide was used in the study because of the wide variation in furosemide bioavailability. Given

that a larger number of AHF patients are treated with furosemide instead of bumetanide, the applicability of the equation in patients treated with furosemide should be confirmed. Moreover, the study did not test the equation in the AHF cohort and its prognostic value is unclear. Because the early identification of high-risk patients is more crucial in AHF than in the chronic heart failure population, DR with urine output or body weight, which has been clearly shown to be a prognostic predictor in a number of AHF cohorts, might be a more clinically applicable and reliable risk-stratification tool. Finally, accurate measure of urine output in ED setting is not impossible but still challenging, and the feasibility of this strategy should be tested in the future studies.

## Conclusion

DR measured during the first 6 hours of ED arrival based on urine output can predict prognosis as efficiently as DR measured during the first 48 hours in patients with AHF. DR can change over time, and accounting for this change contributes to a better prognostic prediction. Our study results underscore the utility of early DR and repetitive DR evaluation in patients with AHF.

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Figure legends

Figure 1. Study flowchart

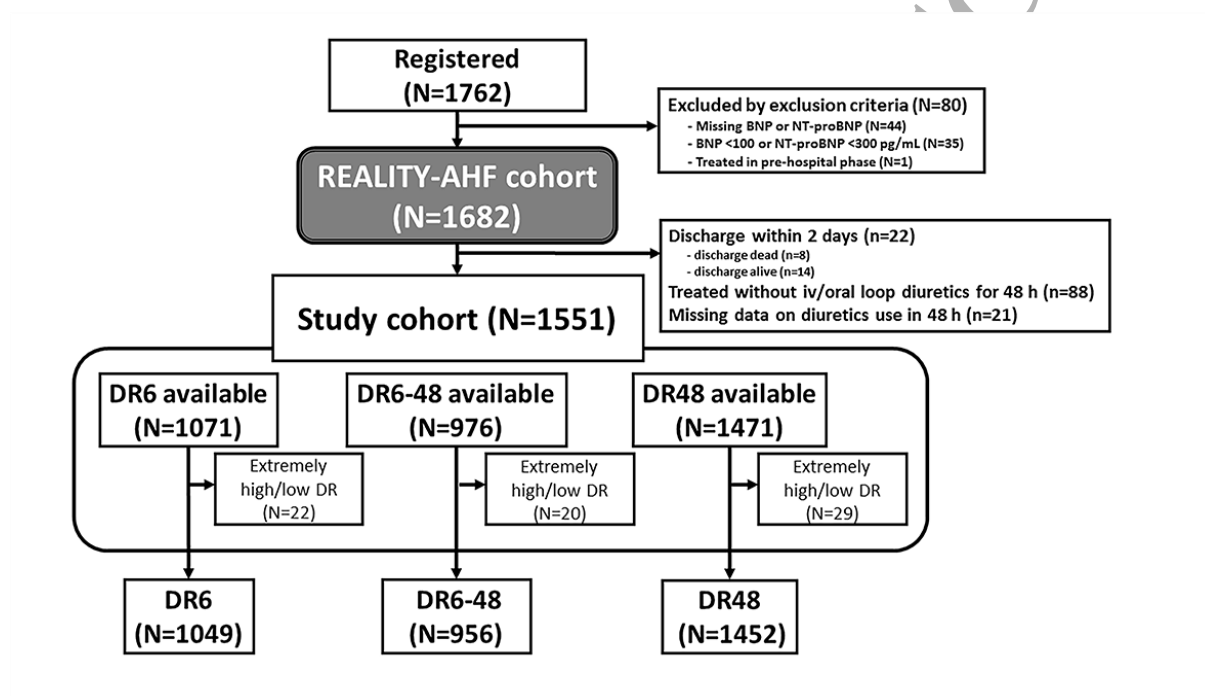
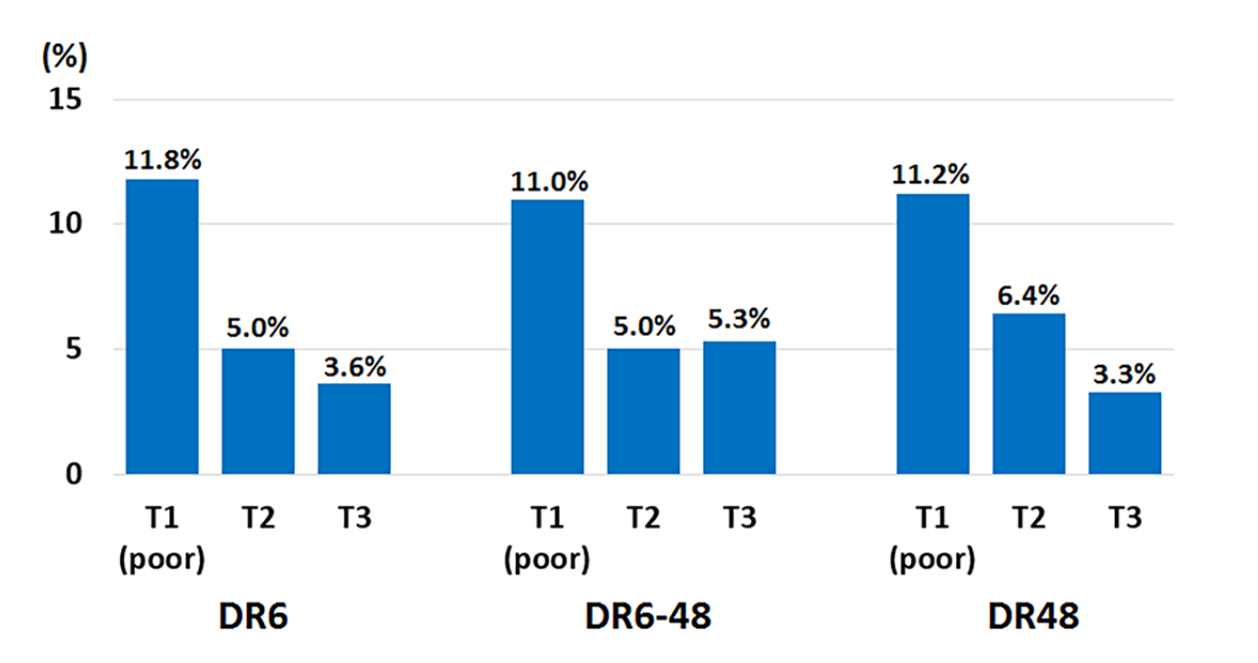
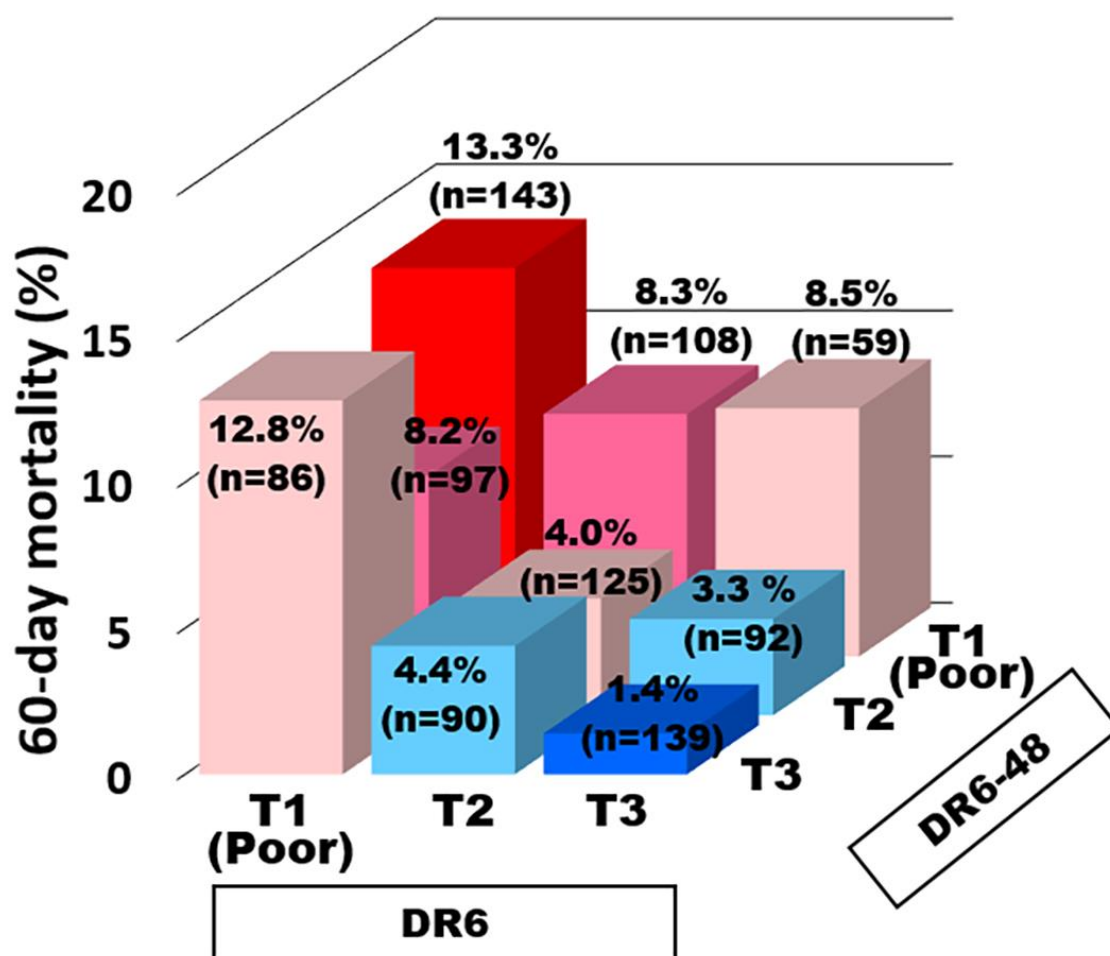


Figure 2. Mortality for 60-day according to the tertiles of DR6, DR6-48, and DR48



DR, diuretic response

Figure 3. 60-day mortality, tertiles of DR6, and tertiles of DR6-48



These plots shows the relationship of 60-day and 180-day mortality to the tertiles of DR6 and DR6-48.

DR, diuretic response

## Tables

Table 1. Baseline characteristics of patients according to DR6

Variables	DR6			P value
	T1 (poor) n=356	T2 n=357	T3 n=336	
Age (years)	80±11	78±11	76±14	<0.001
Male gender (%)	196 (55.1)	193 (54.1)	186 (55.4)	0.937
Arrived by ambulance (%)	226 (63.5)	223 (62.5)	173 (51.5)	0.002
Systolic blood pressure (mmHg)	151±37	152±37	155±31	0.179
Diastolic blood pressure (mmHg)	82±24	86±27	89±24	0.002
Heart rate (bpm)	99±28	98±28	101±29	0.361
NYHA III or IV	307 (89.5)	290 (83.3)	283 (87.1)	0.056
Symptom onset time (%)				0.340
≤ 6 hours	85 (23.9)	85 (23.8)	80 (23.8)	
6 hours - 2 days	94 (26.4)	76 (21.3)	69 (20.5)	
> 2 days	177 (49.7)	196 (54.9)	187 (55.7)	
ECG rhythm (%)				0.703
Sinus	204 (57.5)	197 (55.2)	182 (54.3)	
AF	126 (35.5)	129 (36.1)	131 (39.1)	
Others	25 (7.0)	31 (8.7)	22 (6.6)	
LVEF at ED (%)				0.469
<35%	117 (35.7)	123 (36.6)	111 (35.9)	
35-50%	113 (34.5)	96 (28.6)	92 (29.8)	
>50%	98 (29.9)	117 (34.8)	106 (34.3)	
Physical examination (%)				
JVD	219 (62.8)	226 (63.7)	214 (64.5)	0.898
Orthopnea	254 (71.8)	227 (63.6)	216 (64.3)	0.039
Rale	259 (73.0)	256 (71.7)	232 (69.3)	0.551
Peripheral edema	251 (70.7)	259 (72.5)	256 (76.2)	0.256
Pulmonary edema	281 (78.9)	265 (74.2)	260 (77.4)	0.317
Comorbidities (%)				
History of Heart Failure	193 (54.2)	193 (54.1)	140 (41.7)	0.001
Hypertension	254 (71.3)	233 (65.3)	241 (71.7)	0.113
Diabetes mellitus	130 (36.5)	144 (40.3)	109 (32.4)	0.098
COPD	44 (12.4)	30 (8.4)	37 (11.0)	0.218
Coronary artery disease	118 (33.1)	108 (30.3)	90 (26.8)	0.190
Medication at admission				



(%)

Loop diuretics	206 (57.9)	189 (53.1)	120 (36.3)	<0.001
ACE-I	61 (17.2)	64 (17.9)	54 (16.1)	0.809
ARB	110 (31.0)	118 (33.1)	105 (31.2)	0.813
Beta blocker	158 (44.8)	151 (42.5)	122 (36.4)	0.072
Aldosterone blocker	67 (18.8)	88 (24.6)	57 (17.0)	0.030

#### Laboratory data

WBC (/μl)	8500[6200,11400]	7400[5800,9500]	7300[5600,9225]	<0.001
Albumin (g/dL)	3.4±0.6	3.5±0.5	3.6±0.5	<0.001
Hemoglobin (g/dL)	11.4±2.1	12.0±2.3	12.1±2.4	<0.001
AST (IU/L)	32[23,50]	30[23,45]	34[25,48]	0.192
ALT (IU/L)	20[13,35]	21[14,34.50]	25[17,39.25]	0.002
Creatinine (mg/dL)	1.3[0.9,2.0]	1.2[0.8,1.5]	1.0[0.8,1.3]	<0.001
BUN (mg/dL)	30[22,44]	24[17,31]	21[16,28]	<0.001
Sodium (mEq/L)	139[137,142]	140[137,142]	140[137,142]	0.081
Potassium (mEq/L)	4.4±0.8	4.4±0.6	4.1±0.6	<0.001
Glucose (mg/dL)	171±78	174±82	158±73	0.026
CRP (mg/dL)	0.85[0.30,2.85]	0.59[0.21,1.73]	0.43[0.12,1.46]	<0.001
BNP (pg/mL)	912[494,1641]	702[436,1259]	671[388,1170]	<0.001

#### Length of hospital stay

(days)	16 [10, 28]	16 [10, 25]	16 [11, 24]	0.657
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#### Type of diuretic administered

Furosemide	355 (99)	356 (99)	334 (99)	0.131
Azosemide	5 (1)	11 (3)	4 (1.2)	0.742
Torsaemide	1 (0.3)	3 (0.8)	3 (0.9)	0.542

ACE-I, angiotensin-converting enzyme inhibitor; ALT, aspartate aminotransferase; ARB, angiotensin II receptor blocker; AST, alanine aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ED, emergency department; JVD, jugular venous distention; LVEF, left ventricular ejection fraction; WBC, white blood cell count

Table 2. Multivariate linear regression analysis for DR6, DR6-48, and DR48

Multivariable linear regression for DR6				Multivariable linear regression for DR6-48				MV linear regression for DR6-48 with DR6				Multivariable linear regression for DR48			
(Adjusted R <sup>2</sup> =0.140)				(Adjusted R <sup>2</sup> =0.065)				(Adjusted R <sup>2</sup> =0.088)				(Adjusted R <sup>2</sup> =0.109)			
Variables	Standardized Beta	t value	P value	Variables	Standardized Beta	t value	P value	Variables	Standardized Beta	t value	P value	Variables	Standardized Beta	t value	P value
Creatinine	-0.152	-3.91	<0.001	On diuretics at baseline	-0.171	-5.10	<0.001	DR6	0.204	6.336	<0.001	On diuretics at baseline	-0.199	-7.48	<0.001
Age	-0.151	-4.18	<0.001	CRP	-0.092	-2.83	0.005	On diuretics at baseline	-0.164	-5.105	<0.001	Age	-0.129	-4.67	<0.001
On diuretics at baseline	-0.150	-4.13	<0.001	Rale	-0.079	-2.40	0.016	CRP	-0.098	6.336	<0.001	Systolic blood pressure	0.836	3.18	0.002
WBC	-0.142	-3.95	<0.001	Creatinine	-0.078	-2.39	0.017					ALT	0.079	3.049	0.002

Potassium	-0.104	-2.80	0.005	Systolic blood pressure	0.071	2.10	0.036	Hemoglobin	-0.078	-2.713	0.006
Albumin	0.090	2.47	0.014	Age	-0.064	-1.98	0.048	BUN	-0.077	-2.17	0.029
BNP	-0.073	-2.00	0.046					Creatinine	-0.075	-2.19	0.029

ALT, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; WBC, white blood cell count

**Table 3. Univariate and multivariable Cox regression analysis for 60-day and 180-day mortality**

Variables	60-days mortality					
	Univariate Cox Model			Multivariable Cox Model (*full adjustment)		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Diuretic response in 6 hours						
DR in 6 hours (per 100 mL increase)	0.96	0.94-0.98	0.002	0.95	0.95-0.99	0.021
Diuretic response in 6-48 hours						
DR in 6-48 hours (per 100 mL increase)	0.99	0.98-0.99	0.003	0.99	0.98-0.99	0.045
Diuretic response in 48 hours						
DR in 48 hours (per 100 mL increase)	0.97	0.96-0.99	<0.001	0.98	0.97-0.99	0.002

CI, confidence interval; DR, diuretic response

\*Adjusted for age, gender, New York Heart Association functional class, systolic blood pressure, heart rate, history of heart failure, history of diabetes, left ventricular ejection fraction, prescription of beta blocker, prescription of angiotensin inhibitor or angiotensin II receptor blocker at admission, hemoglobin, serum sodium, serum creatinine, blood urea nitrogen (BUN), BNP, and C-reactive protein.

Table 4. Comparison of AUCs of the DR6, DR48, and DR6+DR6-48 models for 60-day and 180-day mortality and NRI

		Updated model for 60-day mortality	
		DR48 model (AUC: 0.66, 95% CI: 0.61-0.72)	DR6+DR6-48 model (AUC: 0.68, 95% CI: 0.61-0.74)
Baseline model for 60-day mortality	DR6 model (AUC: 0.67, 95% CI: 0.60-0.73)	AUC diff: -0.006, P=0.828 NRI: 0.030, 95% CI: -0.218- 0.277, P=0.815	AUC diff: +0.03, P=0.697 NRI: 0.249, 95% CI: 0.021-0.477, P=0.032
	DR48 model (AUC: 0.66, 95% CI: 0.61-0.72)		AUC diff: +0.03, P=0.596 NRI: 0.287, 95% CI: 0.035-0.538, P=0.025

AUC, area under the curve; NRI, net-reclassification improvement